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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/520,883	08/25/2005	Jorg Peters	Le A 36 075	7044
35969	7590	12/03/2008		
Barbara A. Shimei Director, Patents & Licensing Bayer HealthCare LLC - Pharmaceuticals 555 White Plains Road, Third Floor Tarrytown, NY 10591			EXAMINER LI, RUIXIANG	
			ART UNIT 1646	PAPER NUMBER
			MAIL DATE 12/03/2008	DELIVERY MODE PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/520,883	PETERS ET AL.	
	Examiner	Art Unit	
	RUIXIANG LI	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 29 July 2008.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-19 is/are pending in the application.
- 4a) Of the above claim(s) 18 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-17 and 19 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Status of Application, Amendments, and/or Claims

1. Applicants' amendment filed on 07/29/2008 has been entered. Claim 1-10 are amended. Claims 11-19 are added. Claims 1-19 are pending. Claims 1-17 and 19 are under consideration. Claim 18, which is drawn to a distinct invention from the invention group being examined, is withdrawn from further consideration

Withdrawn Objections and/or Rejections

2. All the rejections set forth in the previous office action are withdrawn in view of amended claims.
3. The objection to claim 9 for minor informality is withdrawn in view of amended claim.

Claim Rejections—35 U.S.C. § 112, 2nd paragraph

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claim 10 is rejected under 35 U.S.C. §112, second paragraph because claim 10 recites the limitation "wherein the artificial chaperone is a cyclic dextrin or linear dextrin" in lines 1-2. There is insufficient antecedent basis for this limitation in the claim.
6. Claim 3 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

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Claim 3 is indefinite because it recites a limitation, "wherein the washing buffer is a non-ionic detergent...". It is well known in the art that a washing buffer cannot be a detergent.

Claim Rejections Under 35 U.S.C. §103 (a)

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

8. Claims 1-6, 8, 11, 13, 14, 17, and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Domingues et al. (Journal of Biotechnology 84:217-230, 2000) in view of Wyllie et al. (U.S. Patent No. 5,932,102, Aug. 3, 1999).

Domingues et al. teach a method for purifying interleukin-4 or mutants by recombinant expression comprising (a) expression in inclusion bodies (page 220, right column, the 3rd paragraph), (b) disrupting the cells and separating the inclusion bodies, (c) washing inclusion bodies obtained with 0.1 M Tris-HCl pH8/1 mM EDTA/0.1% zwittergent, (d) solubilizing the inclusion bodies in 8 M GdnHCl, (e) renaturing the expression product and purifying the expression product by cross-flow ultrafiltration against five volumes of buffer (page 220, right column, the 4th paragraph to page 221, the first paragraph of left column).

Domingues et al. fail to teach steps (e) and (f) of claim 1, .i.e., separating the denatured IL-4 or muteins thereof using an immobilized metal chelate affinity

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chromatography (IMAC) system and releasing the IL-4 or muteins thereof from the IMAC system.

Wyllie et al. teach a method for purifying a protein containing histidine residues using immobilized metal affinity chromatography (Abstract). Wyllie et al. teach that human IL-4 has 5 histidine residues and is predicted to have high affinity to the immobilized metal (bottom of column 3). Wyllie et al. also teach purifying human IL-4 from E. coli. using Zinc-chelating affinity chromatography (columns 5 to 6).

Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the method of Domingues et al. to purify the denatured IL-4 or muteins thereof using an immobilized metal chelate affinity chromatography with a reasonable expectation of success. One would have been motivated to do so because an immobilized metal chelate affinity chromatography provides an alternative approach for purifying IL-4 as demonstrated by Wyllie et al. The purity of interleukin-4 or mutants thereof purified using Zinc-chelating affinity chromatography would necessarily have a purity of about 90% as estimated by SDS-PAGE analysis.

It is also noted that while the cited references do not teach the specific zwitterionic detergents listed in claim 19, it would have been obvious to one having ordinary skill in the art at the time the invention was made to use a zwitterionic detergent, such as CHAPS or zwittergent series, in a washing buffer with a reasonable expectation of success. One would have been motivated to do so

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because a zwitterionic detergent, such as CHAPS or zwittergent series, has been widely used for such a purpose.

9. Claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over Domingues et al. (Journal of Biotechnology 84:217-230, 2000) and Wyllie et al. (U.S. Patent No. 5,932,102, Aug. 3, 1999) as applied to claims 1-6, 8, 11, 13, 14, 17, and 19 above, and further in view of Apeler et al. (EP 1022337 A2, 07/26/2000).

Domingues et al. and Wyllie et al. teach a method for purifying interleukin-4 or mutants by recombinant expression using an immobilized metal chelate affinity chromatography as applied to claims 1-6, 8, 11, 13, 14, 17, and 19 above.

Domingues et al. and Wyllie et al. fail to teach a method for purifying an interleukin-4 mutant, Interleukin-4 R121D Y124D.

Apeler et al. teach expression of a human interleukin-4 mutant, Interleukin-4 R121D Y124D (page 2, paragraphs [0002] and [0007]).

Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to apply the method taught by Domingues et al. and Wyllie et al. to purify interleukin-4 R121D Y124D using an immobilized metal chelate affinity chromatography with a reasonable expectation of success. One would have been motivated to do so because the human interleukin-4 mutants, Interleukin-4 R121D Y124D, comprise 5 histidine residues and would have high affinity to an immobilized metal as taught by Wyllie et al. (bottom of column 3).

10. Claims 9 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Domingues et al. (Journal of Biotechnology 84:217-230, 2000) and Wyllie et al. (U.S.

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Patent No. 5,932,102, Aug. 3, 1999) as applied to claims 1-6, 8, 11, 13, 14, 17, and 19 above, and further in view of Apeler et al. (EP 1022337 A2, 07/26/2000).

Domingues et al. and Wyllie et al. teach a method for purifying interleukin-4 or mutants by recombinant expression using an immobilized metal chelate affinity chromatography as applied to claims 1-6, 8, 11, 13, 14, 17, and 19 above.

Domingues et al. and Wyllie et al. fail to teach the renaturation of interleukin-4 or mutants by dialysis in the presence of an artificial chaperone.

Gellman et al. teach the use of an artificial chaperone, such as β -cyclodextrin for refolding enzymes (see Example 1).

Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the method of Domingues et al. and Wyllie et al. to use an artificial chaperone, such as β -cyclodextrin for refolding interleukin-4 or mutants thereof with a reasonable expectation of success. One would have been motivated to do so because an artificial chaperone, such as β -cyclodextrin, causes the detergents to be sequestered from a protein and detergent complex and allows the protein to achieve the correct folding as demonstrated by Gellman et al. (see, e.g., Example 1).

11. Claim 12 is rejected under 35 U.S.C. 103(a) as being unpatentable over Domingues et al. (Journal of Biotechnology 84:217-230, 2000) and Wyllie et al. (U.S. Patent No. 5,932,102, Aug. 3, 1999) as applied to claims 1-6, 8, 11, 13, 14, 17, and 19 above, and further in view of Bonsch et al. (J. Biol. Chem. 270:8452-8457, 1995).

Domingues et al. and Wyllie et al. teach a method for purifying interleukin-4 or mutants by recombinant expression using an immobilized metal chelate affinity chromatography as applied to claims 1-6, 8, 11, 13, 14, 17, and 19 above.

Domingues et al. and Wyllie et al. fail to teach a method for purifying mIL-4 Q116D and Y119D.

Bonsch et al. teach mIL-4 Q116D and Y119D, the murine homologs of human IL-4 R121D and Y124D (Fig. 8; page 8457, right column).

Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to apply the method taught by Domingues et al. and Wyllie et al. to purify mIL-4 Q116D and Y119D using an immobilized metal chelate affinity chromatography with a reasonable expectation of success. One would have been motivated to do so because mIL-4 Q116D and Y119D, the murine homologs of human IL-4 R121D and Y124D, comprise histidine residues and would have high affinity to an immobilized metal as taught by Wyllie et al. (bottom of column 3).

12. Claims 15 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Domingues et al. (Journal of Biotechnology 84:217-230, 2000) and Wyllie et al. (U.S. Patent No. 5,932,102, Aug. 3, 1999) as applied to claims 1-6, 8, 11, 13, 14, 17, and 19 above, and further in view of US Patent No. 5,739,281 (Apr. 14, 1998).

Domingues et al. and Wyllie et al. teach a method for purifying interleukin-4 or mutants by recombinant expression using an immobilized metal chelate affinity chromatography as applied to claims 1-6, 8, 11, 13, 14, 17, and 19 above.

Domingues et al. and Wyllie et al. fail to teach renaturing the denatured IL-4 or muteins thereof prior to step (f) by matrix-assisted refolding.

US Patent No. 5,739,281 teaches refolding of numerous proteins, including human and murine β 2-microglobulin (Example 1) and human growth hormone (Example 2) by a cyclic folding procedure on Ni^{2+} activated NTA-agarose matrix (Ni^{2+} NTA-agarose).

Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the method of Domingues et al. and Wyllie et al. to use matrix-assisted refolding taught by US Patent No. 5,739,281 wherein the IL-4 remains bound to the IMAC system with a reasonable expectation of success. One would have been motivated to do so because matrix-assisted refolding provides an efficient and alternative approach for refolding of proteins as demonstrated by US Patent No. 5,739,281.

Conclusion

13. No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

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A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ruixiang Li whose telephone number is (571) 272-0875. The examiner can normally be reached on Monday through Friday from 8:30 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, can be reached on (571) 272-0835. The fax number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you

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have questions on access to the Private PAIR system, please contact the Electronic Business Center (EBC) at the toll-free phone number 866-217-9197.

/Ruixiang Li/

Primary Examiner, Art Unit 1646

Ruixiang Li, Ph.D.

December 1, 2008